REMARKS

Claims 1-64 are pending in the application. Claims 1-26, 34, 37 and 41-64 are withdrawn from consideration pursuant to a restriction requirement. Claims 32-33 and 35 are cancelled. Claim 27 is amended herein to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Support for amended claim 27 can be found in the specification at, for example, page 18, paragraph [0066]. New claim 65 is added. Support for claim 65 can be found in the specification at, for example, page 23, paragraph [0079]. The specification is amended at paragraphs [0063] and [0065] to resolve informalities noted by the Office. No new matter has been added by way of the amendments to the claims or the specification. Applicants respectfully request entry of the amendments and reconsideration in view of the following remarks.

Objection Under 37 CFR 1.75(c)

Claims 32-33 have been objected to under 37 CFR 1.75(c) as being in improper dependent form for failing to further limit the subject matter of the parent claim 27. Claims 32-33 are cancelled herein, rendering the objections moot.

In view of the above, Applicants respectfully request the Examiner withdraw the objections to the claims.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 27-33, 35-36 and 38-40 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants have carefully considered the multiple bases for these rejections and respond with the following.

Claim 27:

Claim 27 was rejected because the Examiner alleges the claim is incomplete and appears to omit essential steps related to "determining or monitoring a therapeutic protocol." MPEP §

2172.01. The Examiner also alleges that the preamble phrase "said auto antibody developed" is indefinite, because the identity of one or more object(s) and/or step(s), if any, required to perform "developing" is unclear. Applicants respectfully traverse the rejection. Nevertheless, Claim 27 has been amended to address the concerns raised by the Examiner.

In particular, the phrases in steps c) and d) of original claim 27 which were cited by the Examiner as lacking antecedent basis have been amended to provide proper antecedent support. Step b) of original claim 27, related to assessing the presence and/or level of the natural substance, has been deleted. The preamble phrase noted by the Examiner has been amended to read "wherein said auto antibody production was a result of therapeutic administration of the natural substance," antibody production being a term well understood by those of skill in the art.

As amended, Claim 27 recites "a method of guiding therapeutic decisions" based on assessing the presence of an autoantibody specific for a natural substance produced as a result of therapeutic administration of the natural substance. Step d) of original Claim 27 is amended to recite "basing therapeutic decisions to initiate, terminate or adjust the level of administration of said natural substance to said subject thereon." The revised claim language is supported in the specification; for example, see page 18, paragraph [0066], which describes multiple bases for making therapeutic decisions based on measuring the presence and/or level of therapeutic inactivating compounds in a sample. As described in the specification, therapeutic inactivating compounds frequently comprise a therapeutic inactivating antibody or antibody fragment. See specification, page 4, paragraph [0014].

In light of the amendments to claim 27, applicants respectfully request that the rejection of Claims 27-31, 36 and 38-40 under 35 U.S.C. § 112, second paragraph, for indefiniteness be withdrawn.

Claims 32-33:

Claims 32-33 are cancelled herein, rendering the rejections moot. Therefore, Applicants respectfully request the Examiner withdraw the rejections to claims 32-33 under 35 U.S.C. § 112, second paragraph.

Claim 35:

Claim 35 has been cancelled, and replaced with new claim 65, which recites a method of guiding therapeutic decisions to initiate, terminate, or adjust the level of administration of a therapeutic agent to a subject, based on the presence of an auto-antibody specific for a natural substance, said auto antibody produced as a result of endogenous production or therapeutic administration of said natural substance, wherein the therapeutic agent has an antagonistic biological effect to the biological effect normally exhibited by said natural substance. Claim 65 falls within the scope of Invention II, drawn to methods of guiding therapeutic decision in view of an "assessed auto antibody," as described on page 2 of the Office Action. Support for claim 65 can be found in the specification at, *e.g.*, page 23, paragraph [0079], describing the use of the claimed method to assess auto antibodies to PTH as a basis to guide therapeutic administration of Vitamin D to suppress PTH production. Thus, no new matter has been added to the application by way of claim 65.

In view of the revised language, Applicants respectfully request the Examiner withdraw the rejections of claim 35 under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 102

Claims 27-28, 30-33, 35-36 and 39-40 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Conti-Fine (U.S. 6,759,385). Applicants respectfully traverse the rejection.

"To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim." *Brown v. 3M*, 265 F.3d 1349, 1351, 60

U.S.P.Q.2D (BNA) 1375, 1376 (Fed. Cir. 2001). Anticipation is avoided if any element of the claim is not disclosed in the cited reference. MPEP § 2131.

As the Office notes, Conti-Fine discloses an embodiment describing "a method to inhibit or suppress an antibody-mediated disease that is associated with the administration of an endogenous protein" (*see* Conti-Fine, column 6, lines 61-63), comprising the administration of an epitope peptide (derived from the endogenous protein sequence) in an amount sufficient to suppress or down-regulate the priming and/or activity of T-cells specific for the endogenous protein (Conti-Fine, column 7, lines 15-18, 25-26) in a mammal at risk of, or having, a disease characterized by a decreased amount, or a lack of, the endogenous protein. *See* Conti-Fine, column 7, lines 10-13. Applicants respectfully suggest that the method of Conti-Fine described above fails to disclose essential elements of the instant claims, and thus does not anticipate the claimed invention. Specifically, the method described by Conti-Fine does not disclose obtaining a sample from a subject and assessing said sample for the presence of an auto antibody specific for a natural substance, wherein said auto antibody is produced as a result of therapeutic administration of said natural substance. Further, Conti-Fine also fails to disclose guiding therapeutic decisions based on the presence of said assessed auto antibody in the assessed sample.

Respectfully, portions of the Conti-Fine reference cited by the Examiner as disclosing elements of the claims are unrelated to one another and to the claimed invention. The "samples" referred to in Conti-Fine (*e.g.* column 5, line 67), which the Office alleges correspond to the samples required by step a) of Claim 27, refer to a method of exposing samples comprised of T-cells and antigen presenting cells to a panel of peptides to identify epitope sequences. Such "samples" are unrelated to those of the current claim, which involve assessing samples taken from a subject undergoing therapeutic administration of a natural substance for the presence of an auto antibody to the natural substance.

Step b) of original claim 27 has been deleted. However, Applicants would like to point out that the allegedly analogous section of Conti-Fine (*e.g.* column 23, lines 30-31 and 35-36) also

relates to the identification of peptide epitopes, by identifying and determining antigen sequences to assist in epitope mapping.

Similarly, the section of Conti-Fine cited by the Office as anticipating step c) of original claim 27 (*e.g.* column 24, lines 21-23), refers to a method of identifying peptide epitopes by measuring the *amount* of antibody specific for the antigen at time periods before and after immunization with an epitope peptide, as a way of determining the tolerogenic efficacy of such peptides. This disclosure fails to anticipate step c) of claim 27, which recites assessing a sample for the *presence* of an auto antibody specific to a natural substance, wherein the auto antibody was produced as a result of therapeutic administration of said natural substance.

Finally, with regards to step d) of original claim 27, the Office brings to our attention Conti-Fine, column 7, lines 43-48. Read in context, the portion cited by the Examiner refers to a "therapeutic method, comprising: nasally administering to a mammal having an indication or disease characterized by a decreased amount ... of an endogenous protein, wherein the mammal is subjected to exogenous introduction of the protein..., [and] an amount of an epitope peptide ...effective to suppress an immune response to the exogenously introduced protein." *See* Conti-Fine, column 7, lines 40-48. This disclosure does not anticipate step d) of claim 27, because it does not require assessing the presence of an auto antibody, and therefore does not provide a basis for guiding therapeutic decisions to initiate, terminate or adjust the level of administration of a natural substance based on the presence of such assessed auto antibody.

Respectfully, with respect to claim 31, the portion of Conti-fine cited by the Examiner as describing a sandwich assay (*e.g.* column 24, line 7) does not anticipate the claim. Claim 31 recites the method of claim 27, wherein the auto antibody is assessed by a sandwich assay format. The immunospot ELISA assay referred to in Conti-Fine is utilized to analyze cytokine secretion after administration of an epitope peptide to specific CD8+ or CD4+ T cell lines, and does not involve the assessment of auto antibodies.

Finally, with respect to claims 39-40, the portions of Conti-Fine cited by the Office, (*e.g.* column 23, lines 30-31 and 35-36), refer to the identification and characterization of the amino acid sequence of an antigen, and using that sequence to design epitope peptides. *See* Conti-Fine, column 23, lines 36-42. The methods of claims 39-40 require assessing the presence of an auto antibody (not the identification and sequencing of an antigen useful to elicit an antibody), and are thus not anticipated by the cited portions of Conti-Fine. Moreover, the 20 residue epitope peptides described by Conti-Fine do not constitute a "natural substance bound by a low molecular weight label" as required by claim 39 (and dependent claim 40). *See, e.g.,* Conti-Fine, column 23, lines 36-37.

Because Conti-Fine fails to anticipate each and every limitation of the claimed invention, Applicants respectfully request that the rejection of Claims 27-28, 30-33, 35-36 and 39-40 under 35 U.S.C. § 102(e) be withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 29 and 38 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Conti-Fine (U.S. 6,759,385) in view of Bunn, 346 N. ENGL. J. MED. 522 (2002). Claim 29 recites the method of claim 27, wherein the natural substance is selected from the group provided in Table 2. Claim 38 recites the method of claim 27, wherein the natural substance is erythropoietin. Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The references cited by the Office do not meet this test, because they fail to teach all the limitations of the claimed invention, and provide neither a motivation nor a reasonable expectation of success that would lead one of ordinary skill in the art to combine the cited references to achieve the claimed invention.

The Office alleges that Conti-Fine teaches a method for determining a therapeutic protocol substantially as described in claim 27 and dependent claims 29 and 38. Additionally, the Office alleges that it would have been obvious to one of ordinary skill in the art to apply the method of determining a therapeutic protocol, as described by Conti-Fine, to erythropoietin in view of Bunn. Applicants respectfully disagree.

As discussed in detail above, Conti-Fine does not teach all the limitations of the claimed invention, and thus does not provide a method for determining a therapeutic protocol substantially as described by the present invention. The methods disclosed in Conti-Fine and cited by the Office mainly relate to the identification and characterization of epitope peptides, and the use of such peptides to inhibit T cell mediated immune responses to exogenously administered proteins. *See*, Conti-Fine, column 6, lines 61-63; column 7, lines 15-18 and 25-26. Conti-Fine specifically fails to disclose the following elements of the claimed method: obtaining a sample from a subject undergoing therapeutic administration of a natural substance; assessing said sample for the presence of a specific auto antibody produced as a result of administration of said natural substance; and guiding therapeutic decisions, including the decision to initiate, terminate or modify therapeutic administration of a natural substance, based on the presence of said assessed auto antibody. *See* Remarks, *supra*, pages 18-20.

The Office further asserts that Bunn describes a method of deciding to initiate or terminate administration of erythropoietin based on an immune response to epoetin. Applicants respectfully disagree. The cited portion of Bunn refers to an article by Casadevall *et al.*, describing a rare but serious side effect in a small group of renal failure patients treated with epoetin, who developed red-cell aplasia and severe anemia because of a drug-induced autoimmune response. *See* Bunn, page 522, left column, paragraph 3. Because the anemia in the epoetin treated patients was much more severe than anemia from chronic renal failure alone, Casadevall *et al.* deduced that the antibody must not only react with epoetin, but must also cross-react with endogenous erythropoietin. *See* Bunn, page 522, right column, paragraph 2 (discussing Casadevall *et al.* N. ENGL. J. MED, 469-475 (2002)).

While the potential for an autoimmune response to exogenously administered erythropoietin was described by Bunn (citing Casadevell *et al.*), this standing alone is insufficient to render the claimed invention obvious. The Office must still provide a motivation to combine Bunn with the disclosure in Conti-Fine, as well as a reason to believe that such a combination would be successful.

The Examiner appears to suggest that a motivation to combine can be found in Bunn's statement that "about 3 million patients worldwide were being treated with epoetin," as well as his statement that "[t]he clinical picture of rapidly developing transfusion-dependent anemia is so dramatic that such cases are unlikely to escape attention." *See, e.g.,* Bunn, page 522, right column, paragraph 4. Applicants respectfully suggest that the quoted phrases, viewed in context, do not support this contention. Bunn points out that "[g]iven that about 3 million patients worldwide are being treated with epoetin, *the incidence of drug-induced erythroid aplasia is remarkably low.*" *See* Bunn, page 522 (emphasis added). Further, because of the dramatic nature of such adverse events, they are "unlikely to escape attention" by treating physicians. Viewed in this light, Bunn's statements do not provide a compelling motive to develop a method to monitor auto antibody production in subjects undergoing epoetin therapy. Further, for the reasons discussed in detail above, even if one was disposed to develop a method to monitor erythropoietin administration, Conti-Fine (U.S. 6,759,385) does not provide one of ordinary skill in the art with the elements necessary to practice the claimed invention.

In view of the above discussion, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

The Applicants note that upon indication that a generic claim is allowable, the nonelected species that incorporate all of the limitations of the generic claim will also be held allowable. *See* 37 C.F.R. § 1.141, MPEP §§ 806.4(d), and 809.02(a). Moreover, if the designated

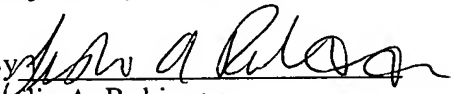
generic claim is determined to be allowable, the Applicants are permitted a reasonable number of species encompassed by this claim. *See* 37 C.F.R. § 1.141; MPEP § 809.02(b).

Applicants expressly reserve the right under 35 U.S.C. § 121 to file a divisional application directed to the nonelected subject matter during the pendency of this application, or an application claiming priority from this application.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532212002000. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 2, 2006

Respectfully submitted,

By 

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